A comparison of single doses of bucindolol and oxprenolol in hypertensive patients

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- 1 Single doses of bucindolol 50, 100 and 200 mg were compared to placebo and single doses of oxprenolol 40, 80 and 160 mg in seven patients with mild hypertension, in a double-blind randomized study.
- 2 Both bucindolol and oxprenolol inhibited exercise induced tachycardia. The mean maximum inhibition of exercise heart rate was similar after each dose of both drugs (20%, $P < 0.001$).
- 3 Bucindolol produced a significantly greater reduction in blood pressure than either oxprenolol or placebo. This was most apparent in standing systolic and diastolic and post-exercise systolic blood pressures between 1 and 2 h after dosing and was dose-related.
- 4 All seven patients experienced adverse effects related to hypotension within the first 2 h after ingestion of bucindolol 200 mg.
- 5 Plasma concentrations of oxprenolol, bucindolol or 5-hydroxy-bucindolol, sampled 2 h after dosing, could not be related to either the changes in blood pressure or to the occurrence of symptoms.
- 6 The results emphasise the need for careful dose-finding of new drugs prior to their more widespread evaluation in phase 3 studies.

Keywords bucindolol 'single dose' effect hypertension oxprenolol

Introduction

Bucindolol is a non-selective β -adrenoceptor blocking drug with intrinsic sympathomimetic activity (Deitchman *et al.*, 1983). Bucindolol may exhibit weak α -adrenoceptor blockade but this has only been observed at high doses (Deitchman *et al.*, 1980). Vasodilator properties of bucindolol have been demonstrated by its effects on reducing perfusion pressure in the canine hind limb preparation (Deitchman *et al.*, 1980) and by its inhibition of pressor responsiveness to angiotensin II (Oates *et al.*, 1981), sug-

gesting a direct vasodilator action. This haemodynamic profile offers theoretical advantages over conventional β -adrenoceptor blocking drugs.

The pharmacokinetic profile of bucindolol is that of a highly protein bound, lipid soluble base which undergoes extensive presystemic hydroxylation in the liver. The elimination half-life is approximately 5 h (Kelman *et al.*, 1984). In terms of its β -adrenoceptor blocking properties and pharmacokinetic profile, bucindolol

appears to be most closely equivalent to oxprenolol among the prescribed β -adrenoceptor blocking drugs.

The aims of our study were to determine single dose 'equivalents' of bucindolol and oxprenolol in terms of suppression of exercise heart rate and to compare the antihypertensive effects of such 'equivalent' doses in hypertensive patients. We anticipated that any ancillary vasodilator action of bucindolol might result in a relatively greater hypotensive effect for the same degree of suppression of exercise heart rate.

Methods

Patients with mild essential hypertension, screened by inpatient assessment (Galloway *et al.*, 1974), took part in the study. Any existing treatment was withdrawn at least 3 weeks prior to the study. Patient exclusions included obstructive airways disease, cardiac failure, peripheral vascular disease, diabetes mellitus, symptomatic ischaemic heart disease, conduction defects on ECG and significant abnormalities of renal or hepatic function on biochemical screening.

Single oral doses of bucindolol, 50, 100 and 200 mg and of oxprenolol 40, 80 and 160 mg and matching placebo were administered according to a double-blind, randomized crossover design. Each dose was administered with a light breakfast. At least 1 week elapsed between consecutive study visits. During the study patients received no other medication.

At each visit blood pressure was measured using the Remler recording system (Scott & Petrie, 1982) and heart rate by ECG recording. Measurements were made after the patient had been supine for 10 min, standing for 3 min, during the last 30 s of treadmill exercise and immediately after cessation of exercise. Each set of measurements was performed at baseline and at hourly intervals for 8 h after tablet ingestion. The exercise load was determined for each patient prior to the study as that required to produce a heart rate of 160 beats min^{-1} during the last 30 s of a 3 min period of exercise. This load was fixed throughout the study. The patients were ambulant in the ward between measurements.

A sample of venous blood sample was drawn 2 h after the ingestion of tablets for measurement of drug concentration in plasma. Plasma concentrations of oxprenolol were measured by gas liquid chromatography with electron-capture detection (Degen & Reiss, 1976) and of bucindolol and 5-hydroxybucindolol by high pressure

liquid chromatography with fluorescence detection (Meredith *et al.*, 1985).

The study was approved by the Grampian Health Board Ethical Committee and all patients gave written informed consent.

Changes in blood pressure and heart rate were evaluated by ANOVA in terms of changes from baseline at each hour, and maximum changes from baseline. Percentage changes and maximum percentage changes in exercise heart rate were also analysed. When an overall *F*-test comparing treatments showed a significant treatment effect ($\alpha = 0.2$), paired treatment comparisons, where appropriate, were performed using the technique of least significant differences ($\alpha = 0.05$).

Results

Six patients completed the study. The remaining patient attended for 6 of the 7 treatment days before defaulting through pressure of work. The available results for this patient are included in the mean data presented.

Some prestudy characteristics of the patients are shown in Table 1. Patient 6 showed normal supine blood pressures during the study although his average supine blood pressure in the 18 months prior to entry had been 162/108 mm Hg, and has subsequently been recorded at 150/90 mm Hg at a follow up visit.

Heart rate

Exercise Mean hourly exercise heart rates are shown in Figure 1. All patients achieved a target heart rate of 160 beats min^{-1} during a pre-study exercise test. The mean baseline exercise heart rate achieved during the study ranged from 135 to 145 beats min^{-1} over the seven randomised treatment sequences. This largely reflects a training effect, the mean (s.d.) baseline exercise heart rate at week 1 being 151 (6) beats min^{-1} and at week 7 being 137 (13) beats min^{-1} . The six active treatments reduced exercise heart rate significantly more than did placebo at every hour post dose (*F* test, $P < 0.0001$) with few exceptions. The mean maximum reduction in exercise heart rate was similar (approximately 20%) for each of the three doses of each drug. However, bucindolol and oxprenolol showed slightly different patterns with time. The effect of bucindolol was maximal between 2 and 3 h and declined very gradually over 8 h, whereas the effect of oxprenolol was maximal between 1 and 2 h and waned rapidly after 4 h, particularly after the 40 and 80 mg doses.

Table 1 Patient characteristics

Patient	Sex	Age (years)	Weight (kg)	Serum creatinine ($\mu\text{mol l}^{-1}$)	Blood pressure (mm Hg)
1	M	33	95.3	101	166/108
2	F	61	60.8	104	189/89
3	M	42	76.2	96	130/93
4	F	44	93.0	60	167/99
5	F	50	89.3	124	165/102
6	M	35	83.0	101	120/84
7	M	56	73.9	80	147/103
Mean		45.9	81.6	95	158/100
s.d.		10.4	12.1	20	27/12

Figure 1 Mean exercise heart rate at baseline and hourly intervals after placebo (●), oxprenolol 40 mg (▲), 80 mg (▼), 160 mg (▴) and bucindolol 50 mg (△), 100 mg (▽) and 200 mg (□). The error bars are omitted for the sake of clarity.

Post-exercise, supine and standing Changes in post-exercise heart rate showed a very similar pattern to those in exercise heart rate. The mean maximum decrease in post-exercise heart rate was approximately 30% after each dose. Oxprenolol was generally accompanied by a decrease in supine heart rate (Table 2). In contrast the three bucindolol doses and placebo were generally accompanied by small mean increases in supine heart rate at every hour post-dose. Although some of the differences and individual dose comparisons were statistically significant, the changes were small (maximum mean increase $9.4 \text{ beats min}^{-1}$ 1 h after bucindolol 200 mg) and of doubtful clinical importance.

Standing heart rate results showed a similar overall pattern to that of supine heart rate, the three oxprenolol doses being accompanied by a small decrease in heart rate, whereas bucindolol

200 mg and placebo were accompanied by a small increase in heart rate.

Blood pressure

Supine Analysis of the mean decreases in supine diastolic blood pressure showed that bucindolol 100 mg and 200 mg produced significantly greater reductions than placebo and all three oxprenolol doses at every hour post dose (Figure 2). When the corresponding changes in supine systolic blood pressure were analysed the differences were statistically significant only at 4 h, although the overall trend was similar. Analysis of mean maximum decreases in supine systolic and diastolic blood pressure from baseline showed that these differences between treatments were not statistically significant (Table 3).

Standing Changes in mean standing blood pressure after placebo, oxprenolol 160 mg and bucindolol 100 and 200 mg are shown in Figure 3. Bucindolol 200 mg produced significantly larger reductions in both systolic and diastolic blood pressure than placebo and oxprenolol 160 mg at 1 and 2 h post-dose. Thereafter the hypotensive effect gradually waned towards 8 h. The mean maximum decreases in standing blood pressure after bucindolol were 26/19 mm Hg (50 mg), 34/28 mm Hg (100 mg) and 54/36 mm Hg (200 mg). The corresponding mean maximum decreases in blood pressure after oxprenolol were 19/10 mm Hg (40 mg), 22/16 mm Hg (80 mg) and 32/19 mm Hg (160 mg) and after placebo 17/19 mm Hg (Table 2). Oxprenolol 160 mg produced a sustained reduction in systolic blood pressure averaging 20 mm Hg between 2 and 7 h that was generally significantly different from placebo and similar to the effects of bucindolol beyond 3 h.

Table 2 Mean changes in supine heart rate (beats min⁻¹) from baseline after placebo, oxprenolol, 40 mg, 80 mg and 160 mg and bucindolol 50 mg, 100 mg and 200 mg. *P* values relate to the overall *F*-test of treatment effects. Treatments with the same letter are not significantly different ($\alpha = 0.05$) on subsequent pairwise treatment comparisons.

Time post-dose (h)	Bucindolol			Oxprenolol			Placebo	<i>P</i> value
	50 mg	100 mg	200 mg	40 mg	80 mg	160 mg		
1	5.1 B,C	2.9 A,B,C	9.4 C	-0.4 A,B	-1.8 A	-0.1 A,B	3.7 A,B,C	0.025
2	5.4	5.1	8.0	1.4	-0.4	-0.1	5.7	0.212
3	3.9	2.3	4.9	-0.9	-2.2	-0.4	2.9	0.219
4	3.7 B,C	1.8 A,B,C	6.0 C	-2.3 A	-2.0 A,B	-0.7 A,B	3.7 B,C	0.037
5	5.7 B,C	4.0 A,B,C	8.3 C	-2.0 A	0.2 A,B	2.1 A,B,C	6.0 B,C	0.080
6	6.3	6.3	4.9	1.1	0.2	0.7	3.1	0.246
7	2.6 A,B	4.0 A,B	5.4 B	3.1 A,B	-0.5 A,B	-2.1 A	4.0 B	0.185
8	2.3 B,C	1.5 A,B,C	3.4 C	1.7 A,B,C	-2.5 A,B	-3.1 A	-2.9 C	0.070

The differences between bucindolol 50 mg, oxprenolol 40 and 80 mg and placebo were not statistically significant.

Exercise It also proved difficult on some occasions to measure blood pressure during exercise with confidence in the accuracy of the readings. Many of the exercise systolic blood pressures in these patients exceeded 250 mm Hg.

Because of a number of unsatisfactory or unobtainable Remler recordings no statistical analysis was performed. However, inspection of the available systolic blood pressures during exercise showed that all six active treatments reduced blood pressure. The greatest fall in blood pressure was seen after bucindolol 100 mg (35%), followed by oxprenolol 160 mg and bucindolol 200 mg (31%).

Figure 2 Mean supine blood pressures, systolic (upper) and diastolic (lower) at baseline and hourly intervals after placebo (●), oxprenolol 160 mg (■), bucindolol 100 mg (▽), and bucindolol 200 mg (□). Representative bars for s.e. mean are shown at 1 h.

Post-exercise Post-exercise blood pressure measurements were obtained from all patients, with two exceptions after bucindolol 200 mg: when the exercise test was abandoned in patient 3 at 2 h and in patient 7 at 1 h because of symptomatic hypotension. The six active treatments reduced blood pressure significantly more than placebo at all hours post dose (*F* test, $P < 0.002$). Bucindolol 200 mg showed the greatest hypotensive effect (Figure 4) and was significantly different from bucindolol 50 mg and oxprenolol 40 and 80 mg. The mean maximum decrease in post-exercise systolic blood pressure after placebo was 10 mm Hg, after oxprenolol 45 mm Hg (40 mg), 53 mm Hg (80 mg), 73 mm Hg (160 mg) and after bucindolol 48 mm Hg (50 mg), 65 mm Hg (100 mg) and 81 mm Hg (200 mg). These maximum reductions in blood pressure occurred between 1 and 3 h post-dose with a gradual return toward baseline thereafter. The mean reduction in post-exercise systolic blood

Table 3 Mean maximum decreases in blood pressure from baseline after placebo, oxprenolol 40 mg, 80 mg and 160 mg and bucindolol 50 mg, 100 mg and 200 mg. *P* values relate to the overall *F*-test of treatment effects. Treatments with the same letter are not significantly different ($\alpha = 0.05$), on subsequent pairwise treatment comparison.

	Placebo	Oxprenolol			Bucindolol			P
		40 mg	80 mg	160 mg	50 mg	100 mg	200 mg	
<i>Supine (mm Hg)</i>								
Systolic	24.6	26.4	28.2	29.0	24.4	35.7	36.4	0.39
Diastolic	19.3	17.0	19.5	17.3	20.7	24.0	25.4	0.44
<i>Standing (mm Hg)</i>								
Systolic	17.4	18.9	22.1	31.9	25.9	33.6	53.9	0.0002
	D	C,D	B,C,D	B,C	B,C,D	B	A	
Diastolic	18.6	10.3	15.6	18.6	18.7	27.7	36.4	0.0001
	C	D	C,D	C	C	B	A	
<i>Post-exercise (mm Hg)</i>								
Systolic	10.1	45.3	53.2	72.6	47.6	65.0	80.7	0.001
	D	C	B,C	A,B	C	A,B,C	A	

pressure from baseline at 8 h was 30 mm Hg after bucindolol 100 and 200 mg.

Many of the post-exercise diastolic blood pressures were at the lower end of the calibration scale on the Remler instrument. Because we have reservations about their accuracy, we have excluded these from formal analysis.

Adverse effects

These are summarised in Table 4. All patients in the study experienced at least one adverse reaction after bucindolol 200 mg. The most fre-

Figure 3 Mean standing blood pressures, systolic (upper) and diastolic (lower), at baseline and hourly intervals after placebo (●), oxprenolol 160 mg (■), bucindolol 100 mg (▽), and bucindolol 200 mg (□). Representative bars for s.e. mean are shown at 1 h.

Figure 4 Mean post-exercise blood pressures, at baseline and hourly intervals after placebo (●), oxprenolol 160 mg (■) and bucindolol 200 mg (□). Representative bars for s.e. mean are shown at 1 h.

quent adverse effects were tiredness of the legs during exercise and dizziness and lightheadness on standing. Two patients felt and looked faint while standing and one during exercise and were asked to lie down to avoid syncope. These symptoms were apparent 1 and 2 h after drug ingestion and each patient subsequently recovered. The symptoms were accompanied both by a profound drop in supine blood pressure from baseline and by postural hypotension. Similar symptoms of lesser degree were experienced after bucindolol 100 mg (two patients) and after oxprenolol 160 mg (one patient).

Table 4 Adverse effects

	Placebo	Bucindolol (mg)			Oxprenolol (mg)		
		50	100	200	40	80	160
Tiredness of legs on exercise ^a	0	0	1	4	1	0	0
Dizziness/lightheaded ^b	0	0	1	2	0	0	1
Presyncope ^c	0	0	0	3	0	0	0
Headache	0	1	0	0	0	1	0
Drowsiness	0	0	0	1	0	0	0
Vomiting	0	0	1	0	0	0	0
Total number of patients	0	1	3	7	1	1	1

^a Tiredness of legs experienced usually during the last minute of treadmill exercise and generally 1–2 h after tablet ingestion.

^b Dizziness/lightheadedness usually experienced after standing for 1–2 min.

^c Presyncope: Two patients felt faint after standing and one during exercise, and looked pale and sweating. On each occasion made to lie down to avoid losing consciousness.

Plasma drug concentrations

The concentrations of oxprenolol, bucindolol and 5-hydroxybucindolol in plasma 2 h after dosing are shown in Table 5.

Considerable interindividual variation was seen in the plasma concentrations of both drugs but there was generally a progressive increase with dose. Further inspection of the data showed no relationship between plasma concentrations of either drug and the changes in blood pressure at 2 h. Neither the plasma concentrations of oxprenolol nor bucindolol bore a relationship to the development of adverse symptoms.

Discussion

This study confirms that bucindolol exhibits β -adrenoceptor blocking properties similar to those

of oxprenolol. The cardioinhibiting dose-response of single doses of bucindolol was relatively flat within the dose range 50–200 mg and resulted in the same (20%) inhibition of exercise heart rate as oxprenolol 40–160 mg. This is compatible with partial agonist activity. The fact that the exercise heart rates achieved during the study were lower than our target of 160 beats min^{-1} is a limitation of this method of exercise, although it allows adequate demonstration of the cardioinhibitory effects of β -adrenoceptor antagonists, and emphasizes the importance of randomization.

The most striking finding in this study was the profound symptomatic hypotension occurring 1–2 h after bucindolol 200 mg. This occurred particularly on standing and both during and after exercise and was accompanied by symptoms in every patient. So consistent were these changes

Table 5 Plasma concentrations of oxprenolol, bucindolol and 5-hydroxybucindolol at 2 h after dosing.

Patient	Oxprenolol			Plasma drug concentrations ($\text{ng } \mu\text{L}^{-1}$)					
	40 mg	80 mg	160 mg	Bucindolol			5-OH bucindolol		
				50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
JH	289	850	—	7	17	95	3	4	14
GM	700	856	894	20	67	202	8	17	63
FC	779	490	832	101	41	295	24	10	35
FH	121	172	518	9	16	57	3	5	13
DC	525	323	832	17	15	42	6	8	34
DF	481	827	1006	8	32	157	8	15	53
JB	519	—	1001	7	21	69	7	7	24
Mean	488	586	847	24	39	131	8	9	34
s.d.	226	300	179	34	19	92	7	5	19

in blood pressure that we felt obliged on ethical grounds to terminate the study on completion of the initial 'block' of seven patients.

The resultant restriction in statistical power does not diminish the clinical importance of the results. The steep hypotensive dose-response of bucindolol contrasts with its flat cardioinhibiting dose-response and with the smaller hypotensive response to 'equivalent' cardioinhibitory doses of oxprenolol. This haemodynamic profile is compatible with an ancillary vasodilator action although the mechanism remains uncertain.

We cannot be sure that our data reflect a true 'first dose' phenomenon since we studied only single doses. Postural hypotension was noted within a few hours of initiating bucindolol by Rotmensch *et al.* (1984). A few other clinical investigators have encountered occasional symptomatic hypotension during the course of early clinical studies with bucindolol. 'First dose' hypotension has been a feature of drugs with α -adrenoceptor blocking properties such as phentolamine (Galloway *et al.*, 1975) and prazosin (Graham *et al.*, 1976). α -adrenoceptor blockade may also be partly responsible for the high frequency of adverse symptoms when labetalol is added to a diuretic in severe hypertension, particularly at inappropriately high initial doses (McArdavey *et al.*, 1984). However, evidence from human studies suggests that α -adrenoceptor blockade is not a significant attribute of bucindolol at these doses (Deitchman *et al.*, 1980).

Postural hypotension is not a feature specific to α -adrenoceptor blockade and may occur with a variety of drugs with different pharmacological properties, e.g. adrenergic neurone blocking drugs, methyl dopa, diuretics and angiotensin converting enzyme inhibitors. Direct acting arteriolar dilators such as hydralazine and calcium channel antagonists are not notable for causing either a 'first dose' effect or postural hypotension, but venodilator agents, such as nitrates,

may do so. Further studies are required to elucidate the mechanisms underlying the hypotensive action of bucindolol.

Our results also further dispel the common misconception that the antihypertensive effect of β -adrenoceptor antagonists is not evident for several days after starting treatment. A hypotensive effect of both oxprenolol and bucindolol appears within 2 h of a single oral dose. This effect may be small and may not represent the maximal response but is quite clearly present on analysis of standing and post-exercise systolic pressures. These observations are consistent with other studies showing rapid hypotensive effects of single doses of propranolol (Galloway *et al.*, 1976) and atenolol (Webster *et al.*, 1984).

Our study was not designed to evaluate the pharmacokinetics of bucindolol. However, the 2 h sampling time coincided with the estimated maximal haemodynamic effects of bucindolol. Previous studies have suggested that peak plasma levels are achieved within 1 h of ingestion of both bucindolol (Kelman *et al.*, 1984) and oxprenolol (Reiss *et al.*, 1975). The possibility exists that bucindolol may exhibit non-linear kinetics. Our limited pharmacokinetic data are compatible with this hypothesis, but do not otherwise provide any obvious concentration-effect explanation for the profound effects of bucindolol on blood pressure.

Our study emphasizes the need for careful dose-finding and clinical evaluation of new drugs prior to their use in phase 3 studies.

Oxprenolol assay was performed by Dr G. M. Hawksworth and G. Cameron, Department of Therapeutics and Clinical Pharmacology, University of Aberdeen and bucindolol/5-OH bucindolol assays by Dr P. Meredith, Department of Materia Medica, Stobhill Hospital, Glasgow. The study was supported by Bristol-Myers Company.

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